

CLAIMS

1. A pharmaceutical composition for oral administration comprising PTH, wherein the *in vitro* release of PTH – when tested in a dissolution test of pharmacopoeia standard – is delayed with at least 2 hours and once the release starts, at least 90% w/w such as, 5 e.g., at least 95% or at least 99% of all PTH contained in the composition is released within at the most 2 hours.
2. A pharmaceutical composition according to claim 1, wherein – when tested in an *in vitro* dissolution test employing 0.1 N HCl equilibrated at 37 °C as the dissolution 10 medium – at the most about 10% w/w such as, e.g., at the most about 7.5% w/w, at the most about 5% w/w, at the most about 2.5% w/w, at the most about 1% w/w of PTH contained in the composition is released 2 hours after start of the test.
3. A pharmaceutical composition according to claim 1 or 2 for delivery of PTH to the 15 small intestine and/or to the colon.
4. A pharmaceutical composition according to any of the preceding claims for delivery of PTH to the jejunum.
5. A pharmaceutical composition according to claim 4, wherein – when tested in an *in vitro* dissolution test employing a dissolution medium having a pH of about 6.8 and a temperature of about 37 °C – the following dissolution patterns of PTH are obtained (after start at pH 6.8): 20
at 15 min. approx. 20% w/w (limits 0-50 % w/w)
at 30 min. approx. 80% w/w (limits 25-100% w/w)
at 60 min. approx. 100 % w/w (limits 50-100% w/w)
6. A pharmaceutical composition according to any of claims 1-3 for delivery of PTH to 30 ileum.
7. A pharmaceutical composition according to claim 6, wherein – when tested in an *in vitro* dissolution test employing a dissolution medium having a pH of about 6.8 and a 35 temperature of about 37 °C – the following dissolution patterns of PTH are obtained (after start at pH 6.8):

at 2 hours 30 min approx. 20% w/w (limits 0-50 % w/w)
at 3 hours 30 min approx. 80% w/w (limits 25-100% w/w)
at 4 hours 30 min approx. 100% w/w (limits 50-100% w/w).

5

8. A pharmaceutical composition according to any of claims 1-3 for delivery of PTH to colon.

9. A pharmaceutical composition according to claim 8, wherein – when tested in an *in vitro* dissolution test employing a dissolution medium having a pH of about 6.8 and a temperature of about 37 °C – the following dissolution patterns of PTH are obtained (after start at pH 6.8):

at 4 hours approx. 20% w/w (limits 0-50 % w/w)
15 at 5 hours approx. 80% w/w (limits 25-100% w/w)
at 6 hours approx. 100 % w/w (limits 50-100% w/w).

10. A pharmaceutical composition according to any of the preceding claims, wherein PTH is recombinant or of mammalian origin including human and is selected from full-length PTH (1-84) or its amino terminal fragment, PTH (e.g. PTH 1-34 etc).

11. A pharmaceutical composition according to any of the preceding claims further comprising a calcium-containing compound.

25 12. A pharmaceutical composition according to claim 11, wherein – when tested in an *in vitro* dissolution test employing 0.1 N HCl equilibrated at 37 °C as the dissolution medium – the following dissolution pattern of calcium is obtained:

at 15 min. approx. 20% w/w (limits 0-50% w/w)
30 at 30 min. approx. 80% w/w (limits 25-100% w/w)
at 45 min. approx. 100 % w/w (limits 50-100% w/w).

35 13. A pharmaceutical composition according to claim 11 or 12, wherein the calcium-containing compound is selected from the group consisting of bisglycino calcium, calcium acetate, calcium carbonate, calcium chloride, calcium citrate, calcium citrate malate, calcium cornate, calcium fluoride, calcium glubionate, calcium gluconate,

calcium glycerophosphate, calcium hydrogen phosphate, calcium hydroxyapatite, calcium lactate, calcium lactobionate, calcium lactogluconate, calcium phosphate, calcium pidolate, calcium stearate and tricalcium phosphate.

- 5 14. A pharmaceutical composition according to any of the preceding claims further comprising a vitamin D (e.g. vitamin D₃).
- 10 15. A pharmaceutical composition according to any of the preceding claims comprising a further therapeutically and/or prophylactically active substance that is effective in bone related disorders.
16. A pharmaceutical composition according to any of the preceding claims further comprising an absorption enhancer.
- 15 17. A pharmaceutical composition according to any of the preceding claims further comprising a PTH-stabilizing agent.
- 20 18. A pharmaceutical composition according to any of the preceding claims in the form of a solid dosage form including tablets, capsules and sachets.
- 25 19. A pharmaceutical composition according to any of the preceding claims in the form of a multiple unit dosage form comprising a multiplicity of the same or different pellets or granules.
- 30 20. A pharmaceutical composition according to any of the preceding claim comprising one or more of a first type of unit, the first type of unit comprising PTH, and the first type of unit having a layered structure of at least
 - i) an inner core
 - ii) a time-controlled layer surrounding the inner core,
 - iii) a film coating applied on the time-controlled layer, wherein the film coating is substantially water insoluble but permeable to an aqueous medium, and
 - iv) an outer layer of an enteric coating.
- 35 21. A pharmaceutical composition according to claim 20, wherein the release of the active substance from the unit - when tested *in vitro* as an average of at least three determinations - is not more than about 10% w/w at a first pH value below about 4.0,

and at a second pH value of from about 5.0 to about 8.0 the active substance is released in such a manner that - after a lag time of from about 0.5 to about 8 hours in which first time period not more than about 10% w/w of the active substance is released - at least about 50% w/w of the active substance contained in the unit is

5 released within a second time period of not more than about 2 hours.

22. A composition according to claim 21, wherein the release of the active substance from the unit - when tested *in vitro* - is not more than about 7.5% w/w such as, e.g., not more than about 5% w/w, not more than about 2.5% w/w or not more than about 1% w/w at the first pH value below about 4.0.

10 23. A composition according to claim 21, wherein the first pH value is below about 3.5, such as, e.g., below about 3.0, below about 2.5, below about 2.0, below about 1.5 or a pH value corresponding to that of 0.1 N HCl.

15

24. A composition according to any of claim 20-23, wherein the lag time is from about 1.0 to about 7 hours such as, e.g., from about 1.5 to about 6 hours, from about 2.0 to about 5 hours or from about 2.5 to about 4.5 hours or from about 2.5 to about 4 hours.

20

25. A composition according to any of claim 20-24, wherein - after said lag time - at least about 60% w/w such as, e.g., at least about 70% w/w, at least about 75% w/w, at least about 80% w/w, at least about 85% w/w, at least about 90% w/w, at least about 95% w/w or at least 99% w/w of the active substance contained in the unit is released within the second time period of not more than about 2 hours.

25

26. A composition according to any of claims 21-25, wherein said second time period is not more than about 90 min such as, e.g., not more than about 60 min, not more than about 50 min, not more than about 45 min, not more than about 40 min, not more than about 35 min, not more than about 30 min, not more than about 25 min, not more than

30 about 20 min, not more than about 15 min, not more than about 10 min or not more than about 5 min.

35 27. A pharmaceutical composition according to any of the preceding claims provided with an enteric coating comprising an enteric polymer that has a pH cut off of at the most about 8.0 such as, e.g. in a range of from about 4.0 to about 7.5, in a range of from about 4.5 to about 7.0, from about 4.9 to about 6.9, from about 5.0 to about 6.5,

from about 5.0 to about 6.3, from about 5.0 to about 6.0, from about 5.0 to about 5.9, from about 5.0 to about 5.7, from about 5.0 to about 5.6 or from about 5.0 to about 5.5.

28. A pharmaceutical composition according to any of claims 20-27, wherein the core is

5 selected from pharmaceutically acceptable beads, spheres, granules, granulates, and pellets.

29. A pharmaceutical composition according to claim 28, wherein the lag time is

controlled by the time it takes for the swellable layer to swell to such an extent that the
10 film coating layer is disrupted or destructed.

30. A pharmaceutical composition according to any of claims 20-29, wherein the lag

time is controlled by the thickness and/or composition of the time-controlled layer.

15 31. A pharmaceutical composition according to any of claims 20-30, wherein the lag time is further controlled by the thickness and/or composition of the film coating layer.

32. A pharmaceutical composition according to any of claims 20-31, wherein the disruption or destruction of the film coating layer iii) is substantially independent of pH.

20

33. A pharmaceutical composition according to any of the preceding claims in the form of a multiple unit composition.

25 34. A pharmaceutical composition according to any of claims 1-32 in the form of a single unit composition.

35. A pharmaceutical composition according to any of the preceding claims comprising i) a PTH, ii) a calcium containing compound, and iii) a vitamin D.

30 36. A pharmaceutical composition according to any of claims 1-34 comprising i) PTH or a fragment, analog or derivative thereof, and ii) a vitamin D as active substances.

35 37. A pharmaceutical kit comprising a first and a second component, the first component comprising PTH and the second component comprising a calcium-containing compound, wherein the *in vitro* release of PTH – when tested in a dissolution test of pharmacopoeia standard – is delayed with at least 2 hours and once

the release starts, at least 90% w/w such as, e.g., at least 95% or at least 99% of all PTH contained in the composition is released within at the most 2 hours.

38. A pharmaceutical kit according to claim 37, wherein the first component comprising

5 PTH comprises a composition as defined in any of claims 1-36.

39. A pharmaceutical kit according to claim 37 or 38, wherein the two components are contained in the same or different container.

10 40. A pharmaceutical kit according to any of claims 37-39 further comprising instructions for use of the components.

41. A pharmaceutical kit according to any of claims 37-40 further comprising a third component comprising a second dose of a calcium-containing compound and with

15 instruction for substantially simultaneous oral intake of the first and the second component followed by oral intake of the third component after 2 hours or more such as, e.g., 3 hours or more, 4 hours or more, 5 hours or more, 6 hours or more, 7 hours or more, or 8 hours or more.

20 42. A pharmaceutical kit according to any of claims 37-41 further comprising a vitamin D.

43. A pharmaceutical kit according to claim 42, wherein vitamin D is included as one of the first or second components or as a separate component.

25

44. Use of a parathyroid hormone (PTH) in combination with a calcium-containing compound for the manufacture of a medicament for the treatment or prevention of bone-related diseases, wherein

30 i) an effective amount of a calcium-containing compound is administered to lower the plasma level of endogenous PTH,
ii) an effective amount of PTH is administered to obtain a peak concentration of PTH once the endogenous PTH level is lowered.

35 45. Use according to claim 44, wherein the calcium-containing compound and PTH is contained in the same or separate pharmaceutical compositions.

46. Use according to any of claims 44-45, wherein the calcium containing compound is administered orally.

5 47. Use according to claim 46, wherein PTH is administered at the most 4 hours later than the calcium containing compound.

48. Use according to any of claims 44-47, wherein PTH is administered substantially simultaneous with the calcium containing compound.

10 49. Use according to any of claims 44-48, wherein PTH and the calcium containing compound is contained in a composition as defined in any of claims 1-36 or a kit as defined in any of claims 37-43.

15 50. A method for administering active substances to the small intestine or colon, the method comprises administering to a patient a sufficient amount of a pharmaceutical composition defined in any of claims 1-36, a kit as defined in any of claims 37-43 or a medicament as defined in any of claims 44-49.

20 51. A method for treatment or prevention of a bone related disorder including osteoporosis, the method comprising oral administration to a patient in need thereof a sufficient amount of PTH in a pharmaceutical composition as defined in any of claims 1-36, a kit as defined in any of claims 37-43 or a medicament as defined in any of claims 44-49.